의학박사 학위논문

복강경 수술을 받는 환자에서 신경자극기 사용 하에서의 수술 후 잔여근이완: 네오스티그민과 슈가마덱스의 비교

Postoperative Residual Neuromuscular Blockade after Reversal Based on a Qualitative Peripheral Nerve Stimulator Response: A Randomised Controlled Trial

2020년 8월

서울대학교 대학원

임상의과학과

이 예 지

A thesis of the Degree of Doctor of Medical Science

Postoperative Residual Neuromuscular Blockade after Reversal Based on a Qualitative Peripheral Nerve Stimulator Response: A Randomised Controlled Trial

August 2020

Seoul National University College of Medicine

Department of Clinical Medical Sciences

Yea-Ji Lee

복강경 수술을 받는 환자에서 신경자극기 사용 하에서의 수술 후 잔여근이완: 네오스티그민과 슈가마덱스의 비교

지도교수 오 아 영

이 논문을 의학박사 학위논문으로 제출함

2020년 5월

서울대학교 대학원

임상의과학과

이 예 지

이예지의 박사 학위논문을 인준함

2020년 7월

위 원 장	홍 성 규	(인)
부위원장	오 아 영	(인)
위 원	공 현 식	(인)
위 원	이 정 림	(인)
위 원	전 영 태	(인)

학위논문 원문 이용에 대한 동의서

본인은 아래의 학위논문이 제3자의 권리를 침해하지 않았음을 서약하며, 서울대학교가 다음과 같이 저작물을 이용하는 것에 동의합니다.

논문 제목	**복강경 수술을 받는 환자에서 신경자극기 사용 하에서의 수술 후 잔여근이완: 네오스티그민과 슈가마덱스의 비교**
학위 구분	**석사□ / 박사 ■**
학 과	임상의과학과
학 번	2017-34533
연 락 처	

1. 본인은 서울대학교가 위 저작물을 인터넷 등 정보통신망을 통해 복제 · 전송 · 배포하는 것에 동의합니다.
2. 본인은 서울대학교가 위 저작물에 대해 무료로 온라인 서비스를 제공하는 것에 동의합니다.
3. 서울대학교는 내용을 변경하지 않는 범위 안에서 위 저작물을 다른 파일 형식으로 변경할 수 있습니다.
4. 본인은 위 저작물의 저작권을 타인에게 양도하거나 출판을 허락하는 등 동의 내용을 변경하고자 할 경우 소속대학(원)에 공개의 유보 또는 해지를 즉시 통보하겠습니다.
5. 서울대학교는 저작권법 및 도서관법을 준수하며 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않습니다.

제 출 일 : 2020 년 7 월 30 일

저 작 자 : 이 예 지 (인)

서울대학교총장 귀하

Abstract

Postoperative Residual Neuromuscular Blockade after Reversal Based on a Qualitative Peripheral Nerve Stimulator Response: A Randomised Controlled Trial

Background: Incomplete recovery of neuromuscular blockade is a common postoperative adverse event in the postanaesthesia care unit.

Objective(s): We examined and compared the incidence of residual neuromuscular blockade when the recommended dose of neostigmine or sugammadex was administered according to the qualitative nerve stimulator response.

Patients: Eighty patients aged between 18 and 69 were included in this study. All patients scheduled to undergo elective laparoscopic cholecystectomy and had an American Society of Anaesthesiologists classification of I or II.

Intervention(s): Patients were randomised to the neostigmine or sugammadex groups. At the end of surgery, the doses of the reversal agents were determined based on the response to the peripheral nerve stimulator, which was discontinued after administration of the reversal agent.

Main outcome measures: The primary outcome was the incidence of postoperative residual neuromuscular blockade. The secondary outcomes were the incidence of

symptoms or signs of residual neuromuscular blockade such as hypoxia, inability to maintain head-lift for 5 s, and diplopia.

Results: The incidence of residual neuromuscular blockade upon arrival in the recovery room was 44.4% in neostigmine group, 0% in sugammadex group. (P <0.0001, relative risk = 1.800, 95% CI 1.355 to 2.411). The incidence of adverse events in the recovery room, such as hypoxia, inability to maintain head-lift for 5 s and diplopia, were low and comparable between the groups.

Conclusion: The incidence of residual neuromuscular blockade upon arrival in the recovery room was significantly higher in the neostigmine group than that in the sugammadex group. However, the incidence of adverse events was similar in neostigmine group and sugammadex group.

.....

Keywords: Postoperative residual neuromuscular blockade

Student Number **: 2017-34533**

CONTENTS

LIST OF TABLES AND FIGURES

Introduction

Postoperative residual neuromuscular blockade (NMB) is detected in up to 50% of patients after use of intermediate acting neuromuscular blocking agents (NMBAs).[1-5] The definition of adequate recovery has been changed over the last few decades, and the current value used as the threshold is a train-of-four (TOF) ratio of 0.9 at the adductor pollicis. Patients who have not recovered to this level are at increased risk for postoperative complications, such as muscle weakness, upper airway obstruction, severe hypoxemia, and pulmonary aspiration, some of which can lead to life-threatening situations.[6] Hence, NMB monitoring is highly recommended whenever NMBAs are administered and the appropriate administration of reversal agents according to the level of paralysis is very important.[7,8]

The use of a quantitative peripheral nerve stimulator (PNS) and measuring the TOF ratio is the only way to ensure adequate neuromuscular reversal and avoid residual NMB after the use of NMBAs. However, everyday practice is far from ideal. A conventional PNS, which is called qualitative subjective monitor, is generally used and only for a minority of patients: recent surveys have shown that qualitative monitoring is done for <40% of patients and that quantitative monitoring is even rarer.[9,10] Hence, current guidelines for the reversal of NMB recommend dosages of reversal agents based on both qualitative and quantitative monitoring results.

We hypothesised that the incidence of postoperative residual NMB upon arrival in the postanaesthesia care unit (PACU) would be higher in patients reversed with neostigmine compared with those reversed with sugammadex when the neostigmine or sugammadex was administered according to the patient's NMB status guided by a qualitative PNS and monitoring was discontinued. The primary outcome was the incidence of postoperative residual NMB upon arrival in the PACU and the secondary outcomes were the time from administration of the reversal agent to

tracheal extubation, the time to the decision to transfer the patient to the PACU, and adverse events in the PACU, such as hypoxia, inability to sustain head-lift for 5 s and diplopia.

Methods

This prospective randomized controlled study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1609/363-002). The trial was registered prior to patient enrolment at clinicaltrials.gov (NCT03292965, principal investigator: Y.J. Lee, date of registration: September 25, 2017). The study was carried out at a single institution after obtaining written informed consent from all subjects. It abided by the Declaration of Helsinki and the Good Clinical Research Practice guidelines for studies of NMBAs.[11]

Patients were eligible for inclusion if they were 18 to 69 years of age, had an American Society of Anesthesiologists classification of I or II, were undergoing elective laparoscopic cholecystectomy, and provided written informed consent. Exclusion criteria were a body mass index $\geq$30 kg m^{-2}, a history of neuromuscular, renal, or hepatic disease, or treatment with drugs known to affect neuromuscular function.

Patients were randomised to receive either neostigmine or sugammadex using a random allocation sequence produced by Random Allocation Software, and the results were sealed in an opaque envelope. Block randomisation (block size of four) was accomplished by a person who was not involved in the study. The attending anaesthesiologists were instructed not to open the allocation envelope until the operation was completed. Hence, they were also blinded to the patient group intraoperatively. Data in the PACU were collected by another investigator who was blinded to the patient groups.

Patients were premedicated in the reception area with intravenous (i.v.) 0.03 mg kg^{-1} midazolam. Routine monitoring, including pulse oximetry, noninvasive blood pressure, and electrocardiography was performed in the operating room. A nerve stimulator (TOF-Watch-SX®;MSDBV,Oss,Netherlands) was applied to monitor the

response of the adductor pollicis muscle. After induction of anaesthesia with i.v. remifentanil and propofol, the TOF-Watch-SX was calibrated and stabilized in following sequence: 1. Apply 1Hz single twitch for 10 s using 50 mA. 2. Apply a 50 Hz tetanic stimulation for 5 s. 3. Using CAL2 function, achieve supramaximal current and adjust twitch height to 100%. 4. Apply TOF stimulation every 12 s for at least 1 min to set stable response. After calibration, 0.6mgkg^{-1} rocuronium was administered via i.v. The trachea was intubated after muscle relaxation was confirmed. Anaesthesia was maintained with desflurane, remifentanil, and rocuronium at the discretion of the attending anaesthesiologist. The TOF-Watch-SX screen was shielded and was used intraoperatively only as a qualitative monitor; that is, movement of the adductor pollicis muscle was monitored by visual or tactile assessments. Remifentanil was discontinued when all gas had left the pneumoperitoneum and the inhaled concentration of desflurane had decreased to 3 to 4% at the start of skin closure and was turned off when the reversal agents were administered at the completion of the operation. At the completion of the operation, NMB was reversed in both groups according to the monitored level of NMB. Reversal of the neostigmine group was done with i.v. 20 μg kg^{-1} neostigmine for a TOF count of 4 without perceived fade, 40 μg kg^{-1} for a TOF count of 4 with fade, and 50 μg kg^{-1} for a TOF count of 2 or 3. When the TOF count was <2, reversal was postponed until a TOF count of 2 was observed. In all cases, i.v. glycopyrrolate was co-administered with neostigmine in a ratio of 1:5. In the sugammadex group, reversal was done with i.v. 2 mg kg^{-1} sugammadex for a TOF count 1 and 4 mg kg^{-1} for a posttetanic count (PTC) ≥1. When PTC was <1, reversal was postponed until the PTC reached ≥1. All doses of neostigmine or sugammadex were based on recent guidelines.[12,13]

Neuromuscular monitoring was done until the administration of reversal agents, and then patients recovered at the discretion of attending anaesthetists without

neuromuscular monitoring. The times to tracheal extubation and patient transfer to the PACU were recorded.

Patients were transferred to the PACU with the TOF-Watch-SX attached. The TOF ratio was assessed upon arrival in the PACU. If the TOF ratio was <0.9, it was measured at 5-min intervals until it reached 0.9. The stimulation current was adjusted to 30 mA. After assessment of the TOF ratio in the PACU, several adverse events, such as hypoxia (defined as SpO_2 <90%), inability to sustain head-lift for 5s and diplopia were evaluated. The adverse events were re-evaluated at 15-min intervals until complete recovery. PACU stay time was also recorded.

The primary outcome was the incidence of postoperative residual NMB, defined as a TOF ratio <0.9 upon arrival in the PACU. The secondary outcomes were the times from administration of the reversal agent to tracheal extubation and to the decision to transfer the patient to the PACU and adverse events at PACU such as hypoxia, inability to sustain head-lift for 5 s and diplopia.

Statistical Analysis

For the sample size estimates, we assumed the incidence of postoperative residual NMB in the neostigmine group to be 35% based on our *a priori* analysis, and a decrease of more than 25% in the incidence in the sugammadex group would be significant. Eighty-six patients were required for a power of 80% at a type 1 error of 5%. Considering a drop-out rate of 10%, 96 patients were planned to be included. However, the interim analysis after including 73 patients showed a significant difference, and the study was stopped.

SPSS software (ver. 25.0; IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The normality of the data distribution was tested using the Shapiro–Wilk test (results not shown). Student's *t*-test was used to compare normally distributed variables, and the Mann–Whitney *U* test was used to compare non-

normally distributed continuous variables. The chi-square test or Fisher's exact test was used to analyze categorical data. All data are expressed as means ± SD, median [range] or as number of patients (%). A *P*-value <0.05 was considered significant. Additionally, standardised differences are reported for the baseline characteristics. Relative risks (RR) and 95% confidence intervals (CI) were calculated for the incidence of postoperative residual NMB.

Results

The subjects were enrolled between September 28 and November 29, 2017. In total, 86 patients were assessed for eligibility. Five patients with BMI >30 kg m^{-2} and 1 patient with neuromuscular disease were excluded, so 80 patients were randomised. After randomisation, four patients in the neostigmine group and three patients in the sugammadex group were excluded due to TOF-Watch-SX mechanical errors. Finally, 73 patients (36 in the neostigmine group and 37 in the sugammadex group) were included in analyses (Figure 1).

The baseline characteristics of the patients were comparable between the groups (Table 1). The incidence of residual NMB upon arrival in the PACU was significantly higher in neostigmine group compared with that in the sugammadex group (44.4% vs. 0%, P <0.0001, RR = 1.800, 95% CI 1.355 to 2.411). Residual NMB remained consistent 5 min later in five patients (13.9% vs. 0%, P = 0.025, RR = 1.161, 95% CI 1.018 to 1.324), and 10 min later in one patient (2.8% vs. 0%, P = 0.493, RR = 1.028, 95% CI 0.973 to 1.087). No patient had postoperative residual NMB 15 min later (Table 2). After reversal of NMB in the operating room, no differences were found in the time to extubation or the time to discharge to the PACU between the groups (Table 3). The mean ± SD TOF ratio upon arrival in the PACU was significantly lower in the neostigmine group compared with that in the sugammadex group (0.87 ± 0.10% vs. 0.97 ± 0.02%, P <0.001). The incidence of adverse events, such as hypoxia, inability to maintain head-lift for 5 s and diplopia, were low and comparable between the groups, and all the adverse events were resolved at the next evaluation after 15 min. PACU stay time was not different between the groups (Table 3).

Figure 1. CONSORT flow diagram.

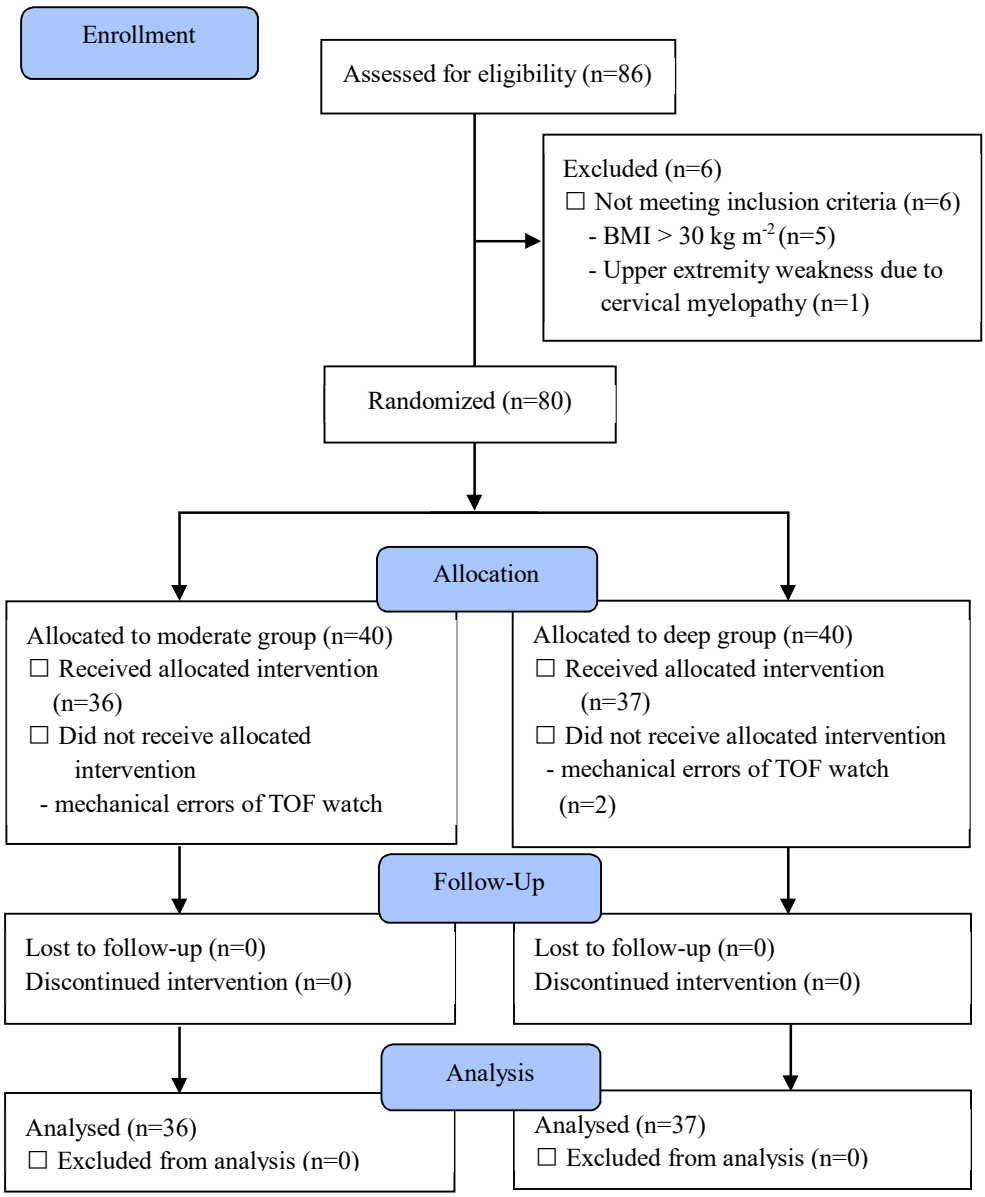

Table 1. Patient Characteristics and Diagnoses.

	Neostigmine (*n*=36)	**Sugammadex (*n*=37)**	***P*-value**	**Standardised differences**
Male, *n* (%)	19 (52.7)	16 (43.2)	0.415	0.192
Age [year]	54 [27 to 83]	57 [33 to 83]	0.380	0.207
Weight (kg)	63.2 ± 13.4	64.3 ± 10.2	0.679	0.097
BMI (kg m^{-2})	23.3 ± 3.4	24.2 ± 3.1	0.285	0.252
ASA score, *n* (%)			0.566	0.135
ASA I	21 (58.3)	24 (64.9)		
ASA II	15 (41.7)	13 (35.1)		

Values are mean ± SD, median [range], or number of patients (%). ASA, American Society of Anesthesiologists. Chi-square test or Student's *t*-test.

Table 2. Postoperative residual neuromuscular blockade at PACU, defined as a Train-of-Four Ratio <0.9, according to the state of neuromuscular blockade at the time the reversal agent was administered.

	Neostigmine				**Sugammadex**
NMB status at reversal	**At arrival**	**5 min**	**10 min**	**15 min**	**At arrival**
TOF0[†]	-	-	-	-	0/8
TOF1	-	-	-	-	0/4
TOF2	11/18	2/18	0/18	0/18	0/6
TOF3	1/1	1/1	0/1	0/1	0/0
TOF4(+)	3/7	2/7	1/7	0/7	0/7
TOF4(-)	1/10	0/10	0/10	0/10	0/12
Total	**16/36 (44.4)[*]**	**5/36 (13.9)[*]**	**1/36 (2.8)**	**0/36 (0)**	**0/37 (0)**

Values are number of patients (%). NMB, neuromuscular blockade; PACU, postanaesthesia care unit; TOF, Train- of-four; TOF4(+), TOF count of 4 with perceived fade; TOF4(-), TOF count of 4 without perceived fade. †: sugammadex was administered only when posttetanic count ≥1, *: P <0.05 *vs.* sugammadex group (Fisher's exact test).

Table 3. Perioperative Outcome Variables.

	Neostigmine (*n*=36)	**Sugammadex (*n*=37)**	***P* Value**
Operation time (min)	51.5 ± 20.8	55.4 ± 30.7	0.973
Anaesthesia time (min)	83.8 ± 24.0	85.1 ± 36.3	0.493
Rocuronium (mg kg^{-1})	0.7 ± 0.1	0.7 ± 0.2	0.262
Neostigmine (μg kg^{-1})	39.8 ± 12.9		
Sugammadex (mg kg^{-1})		2.4 ± 0.8	
Time to extubation (min)	5.5 ± 3.9	5.2 ± 3.5	0.504
Time to discharge to PACU (min)	6.7 ± 3.9	6.6 ± 3.1	0.996
Mean TOF ratio in PACU			
0 min	0.88 ± 0.10	0.97 ± 0.02	<0.001
5 min	0.92 ± 0.06	-	
10 min	0.91 ± 0.02	-	
15 min	0.98 ± 0.00	-	
Train of four ratio <0.9			
0 min (*n*, %)	16 (44.4)	0 (0)	<0.0001
5 min (*n*, %)	5 (13.9)	0 (0)	0.025

10 min (*n,* %)	1 (2.8)	0 (0)	0.493
15 min (*n,* %)	0 (0)	0 (0)	1.0
Symptoms or residual NMB			
Hypoxia (*n*)	2	3	0.430
Head-lift for 5 s (*n*)*	2	2	1.000
Diplopia (*n*)	4	4	1.000
PACU stay time (min)	30.0 ± 7.8	30.4 ± 6.7	0.515

Values are mean ± SD or number of patients (%). PACU, postanaesthesia care unit. *Patients who were unable to maintain head-lift for 5s. Student's *t*-test, Mann–Whitney *U* test or Fisher's exact test were used depending on whether a normal distribution was confirmed.

Discussion

This study demonstrated that the incidence of postoperative residual NMB upon arrival in the PACU was higher in the neostigmine group compared with that in the sugammadex group when the reversal agents were administered according to the patient's NMB status, as guided by a qualitative PNS, and monitoring was discontinued. The incidence of residual NMB upon arrival in the PACU was 44.4% in the neostigmine group and 0% in the sugammadex group.

We administered a reversal agent, neostigmine or sugammadex, to all patients and the dose was determined by the depth of NMB, which was in turn determined by using a PNS. This is different from previous studies on postoperative residual NMB, in the majority of which the reversal agent and/or monitoring of NMB was omitted or only partially used.[1-5] Thilen *et al*.[4] showed that postoperative residual NMB after reversal with neostigmine decreased from 58% to 35% after introduction of the structured protocol. Nemes *et al*.[5] investigated pharmacological reversal based on clinical signs and showed that sugammadex was more effective than spontaneous recovery while neostigmine was not. They also showed that without monitoring, sugammadex also did not guarantee avoidance of residual NMB.

It was somewhat surprising that even with this evidence-based administration of neostigmine, the incidence of postoperative residual NMB was 44.4%, which was not lower compared with previous reports. However, known interindividual variability in recovery from NMB was minimised, and our results showed that all patients recovered to a TOF ratio of >0.9 at 15 min after arrival to the PACU, approximately 30 min after neostigmine administration. It is known that without reversal, the duration of NMB after administration of intermediate-acting NMBAs shows a large interindividual variability that does not recover to a TOF ratio of >0.9,

even after 5 to 6 h in some patients.[2] The mean TOF ratio ± SD in the neostigmine group upon arrival in the PACU was 0.88 ± 0.10, which was similar to the cut-off value of 0.90. This explains why symptoms and signs of residual NMB were rare and were not different between the groups. Further studies with larger numbers of patients might be needed to determine the clinical implications of our results.

The rate of reversal is highly dependent on the depth of NMB at the time of reversal and the dose of reversal agent used. Recent guidelines recommend administering a higher dose of anticholinesterase during a more recovered state: delay reversal when the TOF count <2, 50 to 70 μg kg^{-1} neostigmine if the TOF ratio is <0.4 or the TOF count is 4 with perceived fade, and 20 to 30 μg kg^{-1} if the TOF ratio is >0.4 or the TOF count is 4 without perceived fade.[11,12] Tajaate *et al.*[14] recommended the administration of neostigmine be delayed until an advanced degree of recovery to a T1 >25% of baseline to prevent postoperative residual NMB.

It is difficult to discriminate fade when the TOF ratio recovers to more than 0.4 to 0.5 with conventional qualitative PNS monitoring, and the TOF ratio of 0.4 to 0.9 has been called the 'zone of blind paralysis'.[15,16] Caution is needed when administering neostigmine without the use of quantitative monitoring at this level of NMB, because a high dose of neostigmine can induce muscle weakness if the patient has fully recovered from NMB.[17,18]

However, these are just recommendations, and it has not been shown whether residual NMB can be prevented by simply abiding by these recommendations. Our results demonstrated that even with strict adherence to these recommendations, neostigmine reversal guided by a qualitative PNS could not totally prevent residual NMB. However, all patients recovered to a TOF ratio >0.9 within 30 min after administering neostigmine. Hence, caution is needed for about 30 min after administering neostigmine. No patient showed residual NMB after the use of sugammadex under the same conditions.

The dose and timing of neostigmine administration are still controversial. Patient NMB status is on a continuum, while the recommended doses of neostigmine are not. Hence, the dosage is inappropriate for some patients. Indeed, our previous research revealed that recovery time is significantly shorter when neostigmine is given at a loss of detectable fade to double-burst stimulation than when given at the appearance of the fourth twitch to TOF stimulation when reversing NMB with qualitative PNS.[19] The recovery time from a TOF ratio of 0.5 to 1.0 is significantly shortened by administering 40 μg kg^{-1} neostigmine compared with 20 μg kg^{-1}.[20] Further study is needed to refine the dosage recommendations for neostigmine to reduce postoperative residual NMB.

Several studies have suggested that residual NMB may still occur after administering sugammadex.[4,21,22] However, those studies did not employ or mandate intraoperative neuromuscular function monitoring. The recommended sugammadex dose is based on the status of NMB, and selection of an appropriate dose of sugammadex is not possible without neuromuscular monitoring. Hence, objective monitoring is recommended when using sugammadex as a reversal agent.[9] In this study, no patient in the sugammadex group, where sugammadex was given based on the PNS response, showed residual NMB.

Several limitations in this study should be noted. First, neostigmine was administered after the appearance of a TOF count of 2. The TOF count measured manually by anaesthetists differs from that determined by the TOF-Watch-SX; manual reports tend to be higher.[23] Hence, it is possible that the actual TOF count was <2 when neostigmine was administered. This may have been a factor in our high incidence of postoperative residual NMB. Second, patients and investigators assessing postoperative variables were blinded to the patient group assignments, but the attending anaesthetists knew the group assignments when administering the reversal agents because the timing of administration was different between the

groups. This may have affected several outcome variables, such as the time to extubation and the time to discharge to the PACU. Third, we did not measure the end-tidal concentration of desflurane, and the effect of desflurane may have affected recovery time. The results may have been different with the use of total intravenous anaesthesia. Fourth, we did not use the maximal dose of neostigmine and the possibility exists that the recovery would have improved if the maximal dose of 70 $\mu g\ kg^{-1}$ was used instead of 50 $\mu g\ kg^{-1}$, particularly in patients with TOF count ≤ 4. However, previous reports have shown that reversal of NMB with neostigmine from a TOF count up to 4 was not satisfactory, even in the situation where total intravenous anaesthesia was used with the maximal dose of neostigmine.[24,25] To the last, we used submaximal stimulation of 30mA for measuring TOF ratio in PACU. Submaximal stimulation is often used for measuring TOF ratios in the postoperative period because it is known to be less painful.[11] However, its accuracy is less than with supramaximal stimulation.[26]

Conclusion

The incidence of postoperative residual NMB upon arrival in the PACU was higher in the neostigmine group compared with that in the sugammadex group when the reversal agents were administered under guidance by qualitative PNS but monitoring was discontinued thereafter. However, the incidence of adverse events was minimal and was not different between the groups. Further larger scale studies might be needed to determine the clinical implications of these results.

References

1. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. *Br J Anaesth* 2007; **98**:302-316.
2. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *Anesthesiology* 2003; **98**:1042-8.
3. Fortier LP, McKeen D, Turner K, et al. The RECITE Study: A Canadian prospective, multicenter study of the incidence and severity of residual neuromuscular blockade. *Anesth Analg* 2015; **121**:366-372.
4. Nemes R, Fulesdi B, Pongracsz A, Asztalos L, Szabo-Maak Z, Lengyel S, et al. Impact of reversal strategies on the incidence of postoperative residual paralysis after rocuronium relaxation without neuromuscular monitoring: A partially randomised placebo controlled trial. Eur J Anaesthesiol. 2017; **34**:609-616.
5. Thilen SR, Ng IC, Cain KC, Treggiari MM, Bhananker SM. Management of rocuronium neuromuscular block using a protocol for qualitative monitoring and reversal with neostigmine. *Br J Anaesth* 2018; **121**: 367-377.
6. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg* 2008; **107**:130-137.
7. Oh AY. Monitoring rather than dose matters when using non-depolarising neuromuscular blocking agents. *Br J Anaesth* 2018;**120**: 607.
8. Checketts MR, Alladi R, Ferguson K, et al. Recommendations for standards of monitoring during anaesthesia and recovery 2015: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia* 2016; **71**:85-93.
9. Brull SJ, Kopman AF. Current Status of Neuromuscular Reversal and Monitoring: Challenges and Opportunities. *Anesthesiology* 2017; **126**:173-190.

10. Phillips S, Stewart PA, Bilgin AB. A survey of the management of neuromuscular blockade monitoring in Australia and New Zealand. *Anaesth Intensive Care* 2013; **41**:374-379.
11. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. *Acta Anaesthesiol Scand* 2007; **51**:789-808.
12. Brull SJ, Kopman AF. Current status of neuromuscular reversal and monitoring. Challenges and opportunities. *Anesthesiology* 2017; **126**:173-190.
13. Brull SJ, Murphy GS. Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness. *Anesth Analg* 2010; **111**:129-140.
14. Tajaate N, Schreiber JU, Fuchs-Buder T, Jelting Y, Kranke P. Neostigmine-based reversal of intermediate acting neuromuscular blocking agents to prevent postoperative residual paralysis: A systematic review. *Eur J Anaesthesiol* 2018; **35**: 184-192.
15. Capron F, Fortier LP, Racine S, Donati F. Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanus, 100-hertz tetanus, and acceleromyography. *Anesth Analg* 2006; **102**:1578-1584.
16. Plaud B, Debaene B, Donati F, Marty J. Residual paralysis after emergence from anesthesia. *Anesthesiology* 2010; **112**:1013-1022.
17. Murphy GS, Szokol JW, Avram MJ, et al. Neostigmine Administration after Spontaneous Recovery to a Train-of-Four Ratio of 0.9 to 1.0: A Randomized Controlled Trial of the Effect on Neuromuscular and Clinical Recovery. *Anesthesiology* 2018; **128**:27-37.
18. Kent NB, Liang SS, Phillips S, et al. Therapeutic doses of neostigmine, depolarising neuromuscular blockade and muscle weakness in awake volunteers:

a double-blind, placebo-controlled, randomised volunteer study. *Anaesthesia* 2018; **73**:1079-1089.

19. Song IA, Seo KS, Oh AY, et al. Timing of reversal with respect to three nerve stimulator end-points from cisatracurium-induced neuromuscular block. *Anaesthesia* 2015; **70**:797-802.
20. Choi ES, Oh AY, Seo KS, et al. Optimum dose of neostigmine to reverse shallow neuromuscular blockade with rocuronium and cisatracurium. *Anaesthesia* 2016; **71**:443-449.
21. Kotake Y, Ochiai R, Suzuki T, et al. Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. *Anesth Analg* 2013; **117**:345-351.
22. Martinez-Ubieto J, Ortega-Lucea S, Pascual-Bellosta A, et al. Prospective study of residual neuromuscular block and postoperative respiratory complications in patients reversed with neostigmine versus sugammadex. *Minerva Anestesiol* 2016; **82**:735-742.
23. Bhananker SM, Treggiari MM, Sellers BA, Cain KC, Ramaiah R, Thilen SR. Comparison of train-of-four count by anesthesia providers versus TOF-Watch(R) SX: a prospective cohort study. *Can J Anaesth* 2015; **62**:1089-1096.
24. Kirkegaard H, Heier T, Caldwell JE. Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. *Anesthesiology* 2002; **96**:45-50.
25. Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. *Anesth Analg* 2004; **99**:1080-1085.
26. Helbo-Hansen HS, Bang U, Nielsen HK, Skovgaard LT. The accuracy of train-of-four monitoring at varying stimulating currents. *Anesthesiology* 1992; **76**:199–203.

국 문 초 록

전신 마취 하 수술을 위해 사용하는 신경근 차단제로 인한 수술 후 잔여근이완은 비교적 흔한 부작용 중 하나이다. 수술 후 잔여근이완은 환자의 불편감뿐 아니라 기도 폐쇄, 폐흡인, 폐렴 등 환자의 예후와 관련된 합병증의 발생과 관련이 있다. 복강경 수술의 경우 시야 확보를 위해 수술 중 더 많은 양의 신경근 차단제가 투여되는 경우가 흔하고 이로 인해 복강경을 사용하지 않는 수술에 비해 수술 후 잔여근이완의 발생 가능성도 높다고 할 수 있다. 본 연구에서는 복강경 수술 후 마취 회복 시 신경자극기를 사용하여 지침에서 권고하고 있는 용량대로 역전제 (네오스티그민 vs 수가마덱스)를 투여하였을 경우 수술 후 잔여근이완의 빈도를 비교해 보고자 하였다.

총 80명의 성인 환자를 대상으로 연구를 진행하였고 그 중 73명의 대상자를 분석하였다 (네오스티그민군 대상자 36명, 수가마덱스군 대상자 37명). 수술 종료 후 신경자극기에 대한 반응으로 신경근 차단 정도를 판단하였고 이를 바탕으로 역전제 투여 지침에 따라 용량을 계산하여 네오스티그민과 수가마덱스를 투여하였고 역전제 투여 후부터 대상자가 마취회복실로 퇴실할 때까지는 신경자극기에 대한 반응을 확인하지 않았다. 대상자가 마취회복실로 퇴실한 시점부터 5분 간격으로 15분 동안 수술 후 잔여근이완을 정량적으로 측정하였다. 수술 후 잔여근이완의 발생률은 네오스티그민 군 44.4%, 수가마덱스 군 0%로 두 군 간 유의한 차이가 있었으며 회복실에서 수술 후 잔여근이완으로 인한 합병증의 발생률은 두 군 간 차이가 없었다.

신경자극기에 대한 반응을 바탕으로 지침에 따라 역전제를 투여하여도 네오스티그민을 투여한 대상자는 수가마덱스를 투여한 대상자에 비하여 여전히 높은 수술 후 잔여근이완의 빈도를 보였다. 본 연구의 결과를 토대로 역전제 특히 네오스티그민을 투여할 때는 주의 깊은 용량 선택이 필요하며 신경근 차단 정도에 대한 모니터링이 동반되는 것이 매우 중요하다는 결론을 내릴 수 있다.

……

주요어: 수술 후 잔여근이완

학 번: 2017-34533